



recurrent hydatidiform mole

Recurrent hydatidiform mole occurs when women have at least two abnormal pregnancies described as hydatidiform moles. A hydatidiform mole occurs early in pregnancy when an embryo does not fully develop and the placenta develops abnormally. The placenta is a solid structure in the uterus that normally provides nutrients to a growing fetus. If a hydatidiform mole occurs once, it is known as a sporadic hydatidiform mole; if it happens again, the condition is known as recurrent hydatidiform mole.

A hydatidiform mole often causes vaginal bleeding in the first trimester of the pregnancy. In an ultrasound examination, the abnormal placenta appears as numerous small sacs, often described as resembling a bunch of grapes. In some cases, the ultrasound shows no fetus, umbilical cord, or amniotic sac (a fluid-filled sac that normally surrounds the fetus).

Hydatidiform moles are not naturally discharged from the body and must be surgically removed, typically by the end of the first trimester. After removal, there is up to a 20 percent risk that any tissue left behind (persistent mole) will continue to grow and become a cancerous tumor called an invasive mole. The invasive mole can transform into a different form of cancer called gestational choriocarcinoma that can spread (metastasize) to other tissues such as the liver, lungs, or brain.

Frequency

Hydatidiform moles occur in 1 in 600 to 1,000 pregnancies in western countries and are more common in developing countries. One to six percent of previously affected women will have a recurrent hydatidiform mole.

Genetic Changes

Mutations in the *NLRP7* or *KHDC3L* gene can cause recurrent hydatidiform mole, with *NLRP7* gene mutations being the most common cause.

Within egg cells (oocytes), both the *NLRP7* and *KHDC3L* proteins are thought to play a role in turning off (inactivating) certain genes based on which parent the copy of the gene came from, a phenomenon known as genomic imprinting. For most genes, both copies of the gene (one copy inherited from each parent) are active in all cells. For a small subset of genes, however, only one of the two copies is active; for some of these genes, the copy from the father is normally active, while for others, the copy from the mother is normally active. The *NLRP7* and *KHDC3L* proteins are likely involved in imprinting multiple maternal genes in oocytes, ensuring that they will be inactive in the developing embryo; the corresponding paternal genes are active.

NLRP7 or *KHDC3L* gene mutations result in the production of proteins with impaired function. As a result, multiple genes that contribute to a developing embryo are not imprinted properly, leading to abnormal gene activity (expression) in all pregnancies. Because many genes that would normally be inactive are instead active, embryonic development is impaired, resulting in a hydatidiform mole.

The NLRP7 protein has also been found to play a role in cell growth and division (proliferation) and cell maturation (differentiation). Research suggests that the NLRP7 protein plays an additional role in immune responses by regulating the release of an immune protein called interleukin-1 beta. Normally, the immune system would recognize a hydatidiform mole as a non-growing pregnancy or foreign tissue and signal the body to remove it. Because the impaired NLRP7 protein slows interleukin-1 beta release, the body cannot trigger an immune response to the abnormal pregnancy. Instead, the hydatidiform mole remains in the body. The cause of the retention of the pregnancy in women with *KHDC3L* gene mutations is unclear.

In some cases of recurrent hydatidiform mole, no mutations in either of these genes have been identified. In these instances, the cause of the condition is unknown.

When there is only a single instance of hydatidiform mole, it is often caused by abnormal fertilization of an egg. In sporadic hydatidiform mole, the embryo either receives genetic information only from sperm cells because the egg has no DNA-containing nucleus, or the embryo receives too much genetic information because two sperm cells fertilized one egg.

Inheritance Pattern

This condition is often inherited in an autosomal recessive pattern, which means a woman has to have mutations in both copies of the gene in each of her cells to have recurrent hydatidiform mole pregnancies. Because the mutations are present in all of a woman's cells, including oocytes (which need these genes to promote normal embryonic development), a hydatidiform mole will develop in each pregnancy that occurs with those egg cells.

Other Names for This Condition

- familial biparental hydatidiform mole
- familial recurrent hydatidiform mole
- FRHM

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Hydatidiform mole
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C2931618/>
- Genetic Testing Registry: Hydatidiform mole, recurrent, 2
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0678213/>

Other Diagnosis and Management Resources

- American Cancer Society: Signs and Symptoms of Gestational Trophoblastic Disease
<https://www.cancer.org/cancer/gestational-trophoblastic-disease/detection-diagnosis-staging/signs-symptoms.html>
- MedlinePlus Encyclopedia: Choriocarcinoma
<https://medlineplus.gov/ency/article/001496.htm>
- MedlinePlus Encyclopedia: Hydatidiform Mole
<https://medlineplus.gov/ency/article/000909.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Choriocarcinoma
<https://medlineplus.gov/ency/article/001496.htm>
- Encyclopedia: Gestational Trophoblastic Disease
<https://medlineplus.gov/ency/article/007333.htm>
- Encyclopedia: Hydatidiform Mole
<https://medlineplus.gov/ency/article/000909.htm>

- Health Topic: Female Infertility
<https://medlineplus.gov/femaleinfertility.html>
- Health Topic: Miscarriage
<https://medlineplus.gov/miscarriage.html>
- Health Topic: Tumors and Pregnancy
<https://medlineplus.gov/tumorsandpregnancy.html>

Genetic and Rare Diseases Information Center

- Hydatidiform mole
<https://rarediseases.info.nih.gov/diseases/10263/hydatidiform-mole>

Additional NIH Resources

- National Cancer Institute: General Information about Gestational Trophoblastic Disease
<https://www.cancer.gov/types/gestational-trophoblastic/patient/gtd-treatment-pdq>
- Office on Women's Health: Infertility Fact Sheet
<https://www.womenshealth.gov/publications/our-publications/fact-sheet/infertility.html>

Educational Resources

- Centers for Disease Control and Prevention: Infertility FAQs
<https://www.cdc.gov/reproductivehealth/Infertility/>
- Cleveland Clinic: Gestational Trophoblastic Tumor
<http://my.clevelandclinic.org/health/articles/gestational-trophoblastic-tumor>
- Disease InfoSearch: Hydatidiform mole
<http://www.diseaseinfosearch.org/Hydatidiform+mole/3504>
- Disease InfoSearch: Hydatidiform mole, recurrent, 2
<http://www.diseaseinfosearch.org/Hydatidiform+mole%2C+recurrent%2C+2/8569>
- MalaCards: recurrent hydatidiform mole
http://www.malacards.org/card/recurrent_hydatidiform_mole
- March of Dimes
<http://www.marchofdimes.org/complications/molar-pregnancy.aspx>
- Merck Manual Consumer Version
<http://www.merckmanuals.com/home/women-s-health-issues/cancers-of-the-female-reproductive-system/hydatidiform-mole>
- Orphanet: Hydatidiform mole
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99927

Patient Support and Advocacy Resources

- Heartstrings
<http://www.heartstringssupport.org/>
- RESOLVE: The National Infertility Association
<http://www.resolve.org/>
- Share Pregnancy & Infant Loss Support, Inc.
<http://nationalshare.org/>
- The International Council on Infertility Information Dissemination, Inc. (INCIID)
<http://www.inciid.org/>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22recurrent+hydatidiform+mole%22+OR+%22Gestational+Trophoblastic+Disease%22+OR+%22Hydatidiform+Mole%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28recurrent+hydatidiform+mole%5BTIAB%5D%29+OR+%28familial+hydatidiform+mole%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

OMIM

- HYDATIDIFORM MOLE, RECURRENT, 1
<http://omim.org/entry/231090>
- HYDATIDIFORM MOLE, RECURRENT, 2
<http://omim.org/entry/614293>

Sources for This Summary

- Fallahian M, Sebire NJ, Savage PM, Seckl MJ, Fisher RA. Mutations in NLRP7 and KHDC3L confer a complete hydatidiform mole phenotype on digynic triploid conceptions. Hum Mutat. 2013 Feb; 34(2):301-8. doi: 10.1002/humu.22228. Epub 2012 Nov 2.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23125094>
- Hayward BE, De Vos M, Talati N, Abdollahi MR, Taylor GR, Meyer E, Williams D, Maher ER, Setna F, Nazir K, Hussaini S, Jafri H, Rashid Y, Sheridan E, Bonthron DT. Genetic and epigenetic analysis of recurrent hydatidiform mole. Hum Mutat. 2009 May;30(5):E629-39. doi: 10.1002/humu.20993.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/19309689>

- Mahadevan S, Wen S, Wan YW, Peng HH, Otta S, Liu Z, Iacovino M, Mahen EM, Kyba M, Sadikovic B, Van den Veyver IB. NLRP7 affects trophoblast lineage differentiation, binds to overexpressed YY1 and alters CpG methylation. *Hum Mol Genet.* 2014 Feb 1;23(3):706-16. doi: 10.1093/hmg/ddt457. Epub 2013 Sep 18.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24105472>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3888260/>
- Messaëd C, Chebaro W, Di Roberto RB, Rittore C, Cheung A, Arseneau J, Schneider A, Chen MF, Bernishke K, Surti U, Hoffner L, Sauthier P, Buckett W, Qian J, Lau NM, Bagga R, Engert JC, Coullin P, Touitou I, Slim R; H M Collaborative Group. NLRP7 in the spectrum of reproductive wastage: rare non-synonymous variants confer genetic susceptibility to recurrent reproductive wastage. *J Med Genet.* 2011 Aug;48(8):540-8. doi: 10.1136/jmg.2011.089144. Epub 2011 Jun 9.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21659348>
- Murdoch S, Djuric U, Mazhar B, Seoud M, Khan R, Kuick R, Bagga R, Kircheisen R, Ao A, Ratti B, Hanash S, Rouleau GA, Slim R. Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage in humans. *Nat Genet.* 2006 Mar;38(3):300-2. Epub 2006 Feb 5.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16462743>
- Nguyen NM, Slim R. Genetics and Epigenetics of Recurrent Hydatidiform Moles: Basic Science and Genetic Counselling. *Curr Obstet Gynecol Rep.* 2014 Jan 21;3:55-64. eCollection 2014. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24533231>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3920063/>
- Parry DA, Logan CV, Hayward BE, Shires M, Landolsi H, Diggle C, Carr I, Rittore C, Touitou I, Philibert L, Fisher RA, Fallahian M, Huntriss JD, Picton HM, Malik S, Taylor GR, Johnson CA, Bonthron DT, Sheridan EG. Mutations causing familial biparental hydatidiform mole implicate c6orf221 as a possible regulator of genomic imprinting in the human oocyte. *Am J Hum Genet.* 2011 Sep 9;89(3):451-8. doi: 10.1016/j.ajhg.2011.08.002. Epub 2011 Sep 1.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21885028>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169823/>
- Slim R, Wallace EP. NLRP7 and the Genetics of Hydatidiform Moles: Recent Advances and New Challenges. *Front Immunol.* 2013 Aug 20;4:242. doi: 10.3389/fimmu.2013.00242. eCollection 2013.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23970884>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747449/>
- Williams D, Hodgetts V, Gupta J. Recurrent hydatidiform moles. *Eur J Obstet Gynecol Reprod Biol.* 2010 May;150(1):3-7. doi: 10.1016/j.ejogrb.2010.01.003. Epub 2010 Feb 19. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20171777>

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